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# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Appellants: Kenji Fukudome and Charles T. Esmon

Serial No.: 09/378,261 Art Unit: 1647

Filed: August 20, 1999 Examiner: Stephen Gucker

For: *CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ ACTIVATED C PROTEIN C RECEPTOR*

Assistant Commissioner for Patents
Washington, D.C. 20231

## SUBSTITUTE APPEAL BRIEF

Sir:

Responsive to the Notification of Non-Compliance with 37 C.F.R. 1.192(c) mailed on February 11, 2003 , this is a substitute Appeal Brief to replace the Appeal Brief filed on November 26, 2002. This is an appeal from the final rejection of claims 16-17 and 27-30 in the Office Action mailed March 26, 2002, in the above-identified patent application. A Notice of Appeal was mailed on August 22, 2002. A check in the amount of $215.00 for the filing of this Appeal Brief for a small entity with a one month extension of time along with a petition for a one month extension of time was enclosed with the Appeal Brief filed November 26, 2002. It is believed that no fee is required with this submission. If a fee is required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

## (1) REAL PARTY IN INTEREST

The real parties in interest of this application are the assignee, Oklahoma Medical Research Foundation, and the licensee, Diagnostica Stago.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellants, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 16, 17 and 24-30 are pending, rejected and on appeal. Claims 18, and 22-23 are cancelled. Claims 16, 17 and 27-30 are on appeal. An amendment accompanies this Appeal Brief to rewrite objected to claims 24-26. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment mailed November 20, 2001. A proposed amendment rewriting claim 24 in independent form accompanies this Brief.

## (5) SUMMARY OF THE INVENTION

The invention is based on the discovery of the endothelial cell protein C/activated protein C receptor, or "EPCR", its function, nucleic acid encoding sequence, antibodies thereto, and role in inflammation and coagulation (page 3, line 9 to page 4, line 3). The claims are directed to a method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to EPCR (page 18, lines 23-26; claim 16 as originally filed). This method

entails administering to a patient an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor (claim 16 as originally filed, and page 21, lines 8-12). The compound to be administered can be antibodies or fragments of antibodies to EPCR, nucleic acid sequences inhibiting expression of the EPCR gene, or synthetic or natural compounds other than proteins, peptides or nucleic acid sequences that inhibit binding (claim 17 as originally filed; page 18, lines 28-31; page 24-25, page 26, lines 26-33; page 21, line 19; pages 21-22; pages 29-31; page 32). The compound can be combined in a pharmaceutically acceptable carrier (page 23, lines 14-23), and administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to EPCR (claim 16 as originally filed; page 35-36).

## (6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 16, 17 and 27-30 are enabled as required by 35 U.S.C. § 112, first paragraph, and

(2) whether claims 16, 17 and 27-30 comply with the written description requirement as required by 35 U.S.C. § 112, first paragraph

## (7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in detail below.

## (8) ARGUMENTS

### a) The Claimed Invention

Protein C is a naturally occurring vitamin K-dependent plasma anticoagulant, whose anticoagulant effect is largely due to a rapid inactivation of factors Va and VIIIa. The Protein C molecule, which occurs naturally and is found in the bloodstream, has no biological effect by itself, but during coagulation, the molecule goes through four complex chemical modifications to form endogenous (or naturally occurring) Activated Protein C (APC), a biologically active molecule that has multiple properties, including anti-thrombolytic, anti-inflammatory, and pro-fibrinolytic effects. Protein C inhibits inflammation by reducing the production of IL-1, IL-6, and TNF-α by monocytes.

EPCR is a type I transmembrane receptor that is highly expressed on the endothelium of large blood vessel, and is equally specific for protein C and activated protein C. Binding of protein C to the EPCR inhibits an inflammatory response by the presence of an unusual carbohydrate sequence on protein C that inhibits inflammatory cell adhesion to selectins (page16, line 9). It is suggested that the anti-inflammatory result is due to presentation of protein C/activated protein C to inflammatory cells, or that the APCR-APC complex might cleave biologically active peptides.

The Appellants have discovered, cloned and characterized the receptor for protein C, EPCR, and described methods to generate antibodies/ antibody fragments to EPCR, and methods to design and screen molecules using computer-assisted drug design (sections beginning on pages 23 and 26).

In some situations, it is desirable to enhance the inflammatory response, for example in treating solid tumors. This can be accomplished by modulating Protein C/ Activated Protein C binding to the EPCR to enhance the inflammatory response. Enhancement of the inflammatory response can be achieved by blocking binding of endogenous molecules to EPCR by administering compounds to a subject in need of an enhanced immune response. Representative compounds include non-protein molecules, antibodies to the protein, fragments of antibodies, and peptide fragments of activated protein C including the Gla domain, which is necessary for binding to EPCR.

The appellants submitted a number of papers to demonstrate that one could modulate EPCR activity to modulate the inflammatory response. These were enclosed with the response to restriction requirement mailed April 27, 2001, and include the following:

(1) Taylor, et al., Blood 95:1680 (2000) demonstrates that blocking of the EPCR in a primate model of sepsis using monoclonal antibodies to EPCR greatly enhances the inflammatory response. See also, Taylor, et al., Blood 97(6):1685-1688 (2001)

(2) Kurosawa, et al., J. Immunology 165:4697-4703 (2000), describing the blocking of EPCR binding using soluble EPCR fragments or antibodies to EPCR, greatly enhances the inflammatory response.

(3) Liaw, et al., J. Biol. Chem. 275(11), 8364-8370 (2001) also demonstrates blocking of EPCR binding using soluble EPCR

(4) Joyce, et al., J. Biol. Chem. 276(14):11199-11203 (April 2001) describes inhibiting EPCR by administration of recombinant human activated protein C.

(5) Ye, et al. Biochem. Biophys. Res. Comm. 259, 671-677 (1999) also describes blocking of EPCR with monoclonal antibodies to EPCR.

(6) Shu, et al., FEBS Lettes 477, 208-212 (2000) also shows blocking of EPCR using monoclonal antibodies to EPCR.

(7) Liaw, et al., J. Biol. Chem. 276(11):8364-8370 (2001) shows which sites on EPCR the monoclonal antibodies bind to that block EPCR activity.

(8) Tsuneyoshi, et al., Thromb. Haemost. 85:356-361 (2001) reports that tumors show increased expression of EPCR, and suggest that blocking of EPCR would block tumor progression.

(9) Taylor, et al., Blood 95(5):1680-1686 (2000) shows that EPCR is protective in bacterial sepsis, and that blocking EPCR increases the inflammatory response.

(10) Jian-Ming Gu, Blood 96:841a(#3516) (2000) describes the inhibition of EPCR expression in mice using homologous recombination in ES cells.

These papers were published shortly after filing of this application and rely on the same techniques, reagents and information provided in the patent application, as discussed below. The papers demonstrate clearly that it did not require undue experimentation to use the claimed methods.

**(b) Rejections Under 35 U.S.C. § 112, First Paragraph**

i. Rejection of Claims 16, 17 and 27-30 under 35 U.S.C. § 112, first paragraph

*The legal standard*

The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 U.S.P.Q. 659 (C.C.P.A. 1976). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 13321, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976). Whether undue experimentation is needed is not based upon a single factor; it is a conclusion reached by weighing many factors. These factors have been summarized in *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and include, but are not limited to:

(1) The quantity of experimentation necessary (time and expense);

(2) The amount of direction or guidance presented;

(3) The presence or absence of working examples of the invention;

(4) The nature of the invention;

(5) The state of the prior art;

(6) The relative skill of those in the art;

(7) The predictability or unpredictability of the art; and

(8) The breadth of the claims.

The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to each of these factors. (see M.P.E.P. § 2164.01 (a))

The MPEP further instructs Examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.04.

In a recent decision by the Court of Appeals by the Federal Circuit, the court ruled that in the event that the specification described and enabled various possible species and provided specific information on methods of use, description of one species would enable one of ordinary skill to practice the method pertaining to the genus. Amgen Inc. v. Hoescht Marion Roussel, Inc. 01-1191,-1218- (C.A.F.C.).

As stated in the MPEP §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

*Claim 16 satisfies the enablement requirement*

Claim 16 stands alone as the generic method for enhancing an inflammatory response by blocking protein C binding to the protein C receptor. The Examiner's only argument is that

although the specification is enabling for antibodies and antibody fragments immunoreactive with the receptor, it does not enable making oligonucleotides and receptor fragments to bind EPCR. In this case, the examiner is relying on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. Antibodies and antibody fragments immunoreactive with EPCR satisfy the claim elements of claim 16, in that they block binding of protein C or activated protein C to the receptor by binding to the EPCR. Further, methods of making and administering antibodies and antibody fragments have been described in the section starting on page 21 of the specification to page 23. The specification describes receptor fragments at pages 32-34. As demonstrated by the papers discussed above, this description, along with the sequence for EPCR shown in Figure 4, is all that is needed to make fragments that block binding.

The legal standard has been met.

*Claims 17, 27 and 28 satisfy the enablement requirement.*

Claims 17, 27 and 28 define the compounds to be administered to enhance the inflammatory response by blocking protein C/ activated protein C to the EPCR. The Examiner has rejected the claims that are drawn to compounds other than antibodies and antibody fragments on the basis that there is no description of proteins other than antibodies that block binding. This is not accurate. First, those skilled in the art would have been fully enabled to make all or part of the receptor protein based on the sequence which is disclosed and methods and reagents available from commercial or scientific sources. The specification also enables one

skilled in the art to make protein C, which will also block binding, as demonstrated by assays described at pages 11-12 and Figure 1, and the papers discussed above. Pages 18-19 describe inhibition of EPCR binding by administration of Tumor Necrosis Factor (TNF).

Methods to produce oligonucleotides are described on page 31, lines 11-31 in detail. DNA-protein interactions are known in the art and are the basis for the DNA footprinting assay. There is also evidence in *Bacillus subtilis* demonstrating DNA binding to the cell surface via proteins of a type IV pilus structure. One of skill in the art would be aware of DNA-protein interactions and the ability of using nucleic acid sequences to interact with the EPCR. Synthesis of oligonucleotides are sufficiently described in the specification. Sequences can be screened without undue experimentation using the methods described in the section beginning on page 23.

The use of a DNA fragment for homologous recombination is demonstrated by the papers discussed above. Inhibition of gene expression is described in the application at pages 27-28.

The examiner asserts that making non-antibody blocking compounds that bind EPCR is highly unpredictable because the function of a compound cannot be predicted by its amino acid sequence. The Examiner is wrong. Computer assisted drug design is described in the section beginning on page 26 of the specification. It would only require routine experimentation to design compounds based on modeling the 3-dimensional structure of an amino acid sequence and designing new drugs to interact with that structure. The amino acid sequence is described in the specification. Modeling systems that can be used are described on page 26, lines 26-33. There is sufficient disclosure to enable the development of non-peptide molecules that interact

with the EPCR. Compounds are developed to interact with extracellular domains of the protein therefore satisfying the limitations of claim 16.

There is also a high degree of homology to the CD1 receptor family. Compounds binding to these receptors may bind to the EPCR. Screening these compounds would not require undue experimentation and the screening methods have been described in the specification on page 23. The resulting compounds are easily screened using the screening methods described in the specification. One of skill in the art would not have to undertake undue experimentation to practice the claimed method. The standard for enablement is met.

*Dependent claims 29 and 30 satisfy the enablement requirement*

Claims 29 and 30 further define properties of the compound for administration to a patient in need of treatment. Claim 29 is directed to combining the compound of claim 16 with a pharmaceutically acceptable carrier. Claim 30 defines that the amount required for administration be an effective amount to enhance a protein C-mediated inflammatory response.

This is demonstrated by the examples in the application using antibodies to EPCR and TNF to inhibit binding of EPCR in cell culture.

In summary, appellants describe methods and reagents for the inhibition of binding of EPCR, by antibodies (actually reduced to practice), by EPCR fragments (described in the specification and demonstrated to work using the same methods and reagents in papers published shortly after filing); by other proteins including protein C and tumor necrosis factor (described in the specification and demonstrated to work using the same methods and reagents in papers

published shortly after filing); and by inhibition of expression of EPCR by homologous recombination with the EPCR-encoding nucleic acid sequence described in the application.

ii. Rejection of Claims 16, 17 and 27-30 under 35 U.S.C. § 112, first paragraph

*The legal standard*

To satisfy the written description requirement under 35 U.S.C. 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g. Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116. (MPEP 2163 I.)

The inquiry into adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

It was recently clarified in Enzo Biochem that "the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See *Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification

need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001)

The Federal Circuit found in *Amgen* that "the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, [and] renders Eli Lilly listless in this case." *Amgen*, 126 F.Supp2d at 149, 57 USPQ2d at 1507. The Federal Circuit has extended this decision in ruling that adequate description of one species satisfies the written description for the corresponding genus of compounds. Furthermore, the court ruled that in the event that the specification described and enabled various possible species and provided specific information on methods of use, description of one species would enable one of ordinary skill to practice the method pertaining to the genus.

Appellants have actually reduced to practice, prior to filing of this application, as demonstrated in the application, two species: antibodies to EPCR and a protein, TNF, which block binding by EPCR and thereby enhance inflammation. In papers published shortly after filing, they have demonstrated that soluble EPCR fragments can also be used, as well as another protein, protein C, and nucleic acid molecules that inhibit expression of EPCR. Each of these compounds is described in the application as filed. The subsequent publications merely confirm the truth of appellants' statements with respect to their efficacy. Therefore appellants have complied with the written description requirement as most recently clarified by the Court of Appeals for the Federal Circuit.

*Claims 16 satisfies the written description requirement*

Claim 16 stands alone as the generic method for enhancing an inflammatory response by blocking protein C binding to the protein C receptor. The Examiner's only argument is that while the specification describes methods using antibodies or antibody fragments to bind the EPCR, the specification is silent on using oligonucleotides or receptor fragments for the same purpose. Claim 16 does not recite the claim elements of oligonucleotides or receptor fragments. Sufficient support for the elements of claim 16 is found in the specification in the section on page 21 entitled "Generation of antibodies for diagnostic or therapeutic use" and in claim 16 as originally filed. Claim 16 satisfies the written description requirement of 35 U.S.C. 112, first paragraph.

*Claims 17, 27 and 28 satisfy the written description requirement.*

Claims 17, 27 and 28 define compounds useful in the method of claim 16. The Examiner agrees that antibodies and antibody fragments are sufficiently described in the specification. Methods for preparing receptor fragments are described on page 32, and the full amino acid sequence for EPCR is provided. Attention is drawn to lines 8-14 which state that fragments can be used to "inhibit or compete for binding to the receptor proteins". Methods to produce oligonucleotides are described on page 31, lines 11-31 in detail. The entire nucleotide sequence encoding EPCR is also provided. Therefore these claims satisfy the written description requirement.

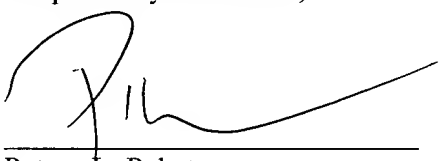
*Dependent claims 29 and 30 satisfy the written description requirement*

Claims 29 and 30 are directed to formulating the compound for administration. There is no mention of oligonucleotides or receptor fragments in these claims. Claim 29 is directed to a pharmaceutical composition wherein the compound is combined in a pharmaceutically acceptable carrier. Claim 30 is directed to an effective concentration to enhance the inflammatory response. The examiner has conceded that at least one species falling within the scope of these claims is fully enabled and complies with the written description requirement. No rejection has been made with respect to the pharmaceutical exicipients *per se*. Therefore, these claims are sufficiently described in the specification and in claims 29, and 30 as originally filed, and therefore satisfy the written description requirement.

## (9) SUMMARY AND CONCLUSION

Claims 16, 17, and 27-30 are sufficiently disclosed and enabled, to satisfy the requirements of 35 U.S.C. 112, and are therefore patentable.

Respectfully submitted,



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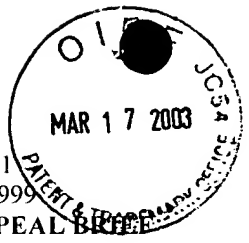


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Patrea Pabst

Date: March 11, 2003

## Appendix I: Claims On Appeal

16. (amended) A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

17. The method of claim 16 wherein the compound is selected from the group consisting of antibodies and fragments of antibodies to the receptor, nucleic acid sequences inhibiting expression of the receptor, and synthetic or natural compounds other than proteins, peptides or nucleic acid sequences which inhibit binding.

24. The method of claim 16 wherein the compound is an antibody or antibody fragment immunoreactive with the receptor.

25. The method of claim 24 wherein the antibody is humanized.

26. The method of claim 16 wherein the compound is labeled.

27. The method of claim 16 wherein the compound is an oligonucleotide.

28. The method of claim 16 wherein the compound is a receptor fragment.

29. The method of claim 16 wherein the compound is combined with a pharmaceutically acceptable carrier.

30. The method of claim 16 wherein the compound is administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor.

## Appendix II: Proposed Amended Claims

16. (amended) A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

17. The method of claim 16 wherein the compound is selected from the group consisting of antibodies and fragments of antibodies to the receptor, nucleic acid sequences inhibiting expression of the receptor, and synthetic or natural compounds other than proteins, peptides or nucleic acid sequences which inhibit binding.

24. A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of an antibody or antibody fragment immunoreactive with the receptor to block binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

25. The method of claim 24 wherein the antibody is humanized.

26. The method of claim 24 wherein the antibody or antibody fragment is labeled.

27. The method of claim 16 wherein the compound is an oligonucleotide.

28. The method of claim 16 wherein the compound is a receptor fragment.

29. The method of claim 16 wherein the compound is combined with a pharmaceutically acceptable carrier.

30. The method of claim 16 wherein the compound is administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor.

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